REMARKS

Discussion of Claim Amendments

Claim 1 has been amended to include the limitations of previous claim 8, which has been now canceled. Claim 1 also has been amended to further refine the preamble. To improve clarity, particularly to distinguish the sub-steps (i-1 to i-5) from the main steps of the claimed method, the term "first step" in claim 1, line 3, has been replaced with --step i)--. Similar replacements were made for the second, third, fourth, and fifth steps, in lines 4, 7, 9, and 11, with step ii), step iii), step iv), and step v), respectively, at the second page of the claim. The term "mixture" in steps iii) and iv) has been replaced with -- immune complex --, to further refine the claim language. Claims 3 and 22 have been amended to include a hyphen between L and chain. New claim 23 has been added and is directed to an embodiment, which is supported, for example, at page 27, lines 2-6 of the specification. No new matter has been added.

Summary of the Office Action

Claims 1, 3-5, 8, and 22 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Claims 1, 3-5, 8, and 22 have been rejected under 35 U.S.C. § 103(a), as allegedly unpatentable over U.S. Patent 5,348,633 (Karger et al.) in view of U.S. Patent 5,630,924 (Fuchs et al.) and *Electrophoresis, 15(1),* 13-21 (1994) (Chen et al.). The Office has rejected claims 2 and 8 under 35 U.S.C. § 103(a), as allegedly unpatentable over Karger et al., Fuchs et al., and Chen et al., and further in view of *Anal. Chem. 66:* 9, 1994 (Shimura et al.) and WO 89/01974 (Bodmer et al.) and U.S. Patent 4,816,567 (Cabilly et al.). Reconsideration of these rejections is hereby requested.

Discussion of Rejections

1. Indefiniteness Rejection

The Office has rejected claims 1, 3-5, 8, and 22 as allegedly indefinite. Applicants have amended claim 1 to provide antecedent basis for the term "the amount of antigen". Claims 3-5, 8, and 22 are dependent upon claim 1. Applicants respectfully submit that the claims are compliant with 35 U.S.C. § 112, second paragraph.

The Office alleges that it is not clear in claim 1 what is encompassed by "antibody...being modified". The Office alleges that it is not clear what the original structure for comparison encompasses. Applicants respectfully submit that the meaning of the term is

clear to those skilled in the art. The Fab' fragment of antibody is obtained by a digestion of antibody with pepsin, which is one of protein digesting enzymes, following reduced reaction. Note the modifications are taking place in the constant region(s) of the antibody. Thus, the antibody can be any antibody possessing the constant regions. Accordingly, applicants respectfully submit that claim meets the clarity requirement under the statute.

The Office also alleges that it is not clear in claim 8 what sequences or characteristics applicant intends as encompassed by "gene". Applicants have canceled claim 8. Claim 1, which now includes the limitations of claim 8, has been drafted with cDNA in place of gene. Accordingly, applicants respectfully submit that claim 1 is clear under the statute.

In view of all of the foregoing, applicants respectfully request that the indefiniteness rejection should be withdrawn.

2. Obviousness Rejection

Claims 1, 3-5, 8, and 22 have been rejected under 35 U.S.C. § 103(a), as allegedly unpatentable over Karger et al. in view of Fuchs et al. and Chen et al. Claims 8 and 22 have been rejected under 35 U.S.C. § 103(a), as allegedly unpatentable over Karger et al. in view of Fuchs et al. and Chen et al. and further in view of Shimura et al., Bodmer et al., and Cabilly et al.

The Office, alleges that Karger et al. teaches a method for quantitative detection of trace amounts of analyte wherein an antibody Fab' fragment specific for the analyte is fluorescently labeled at a single reactive sulfhydryl group in a chemically-modified CH1/hinge region of the fragment, the fragment is reacted with the sample to form an immune complex with any analyte present, the complex is concentrated and separated from unreacted components using capillary electrophoretic methods such as isoelectric focusing, and the concentrated and separated complex is quantitatively detected as an indication of level of analyte by detecting the level of the fluorescent signal of the immune complex. The Office further alleges that the reference implicitly teaches Fab' antibodies having uniform isoelectric points because isoelectric focusing is used to purify the antibody fragments. The Office admits that Karger et al. does not disclose charge-modified antibodies.

The Office, however, alleges that Fuchs et al. teaches that it is well known in the art that the electrophoretic mobility of a labeled antibody in capillary electrophoretic methods could be tailored by attaching charged groups to the labeled antibody. The Office also alleges that Fuchs et al. teaches methods of labeling and charge modification of monoclonal

antibody fragments, for example by the addition of charged amino acid sequences, and teaches that fragments could be purified before use by a method such as isoelectric focusing.

The Office further alleges that Chen et al. teaches that it is possible to achieve effective separation of antigen or antibody from antigen-antibody complexes by modulating the electrophoretic mobility of the antigen or antibody with modification with charge-bearing organic molecules. The Office also alleges that Chen et al. teaches that use of excess modified labeled monoclonal antibody in the capillary electrophoresis methods of the reference would require only a single antibody and obviate the need for a second sandwiching antibody.

The Office contends that it would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have provided a charge-modified labeled monoclonal antibody fragment of uniform isoelectric point in the methods of Karger et al. in view of Fuchs et al. and Chen et al. The Office contends that the process of providing a given reagent does not serve to differentiate an identical reagent provided by another method and that there is nothing on the record which provides evidence of a difference between the antibody fragments of the prior art provided by chemical modifications and those as instantly claimed provided recombinantly.

Although applicants disagree with the rejections, applicants have amended the claims. Applicants respectfully submit that the amended claims are patentable over the cited references. The presently claimed invention provides "a method for quantitatively detecting an antigen using an Fab' antibody being modified *in one molecule* (1) by adding charged amino acid, (2) by being labeled with a fluorescent dye and (3) by modifying amide group-containing amino acid to an amino acid that does not contain an amide group. None of the cited references discloses or suggests to those of ordinary skill in the art the presently claimed invention.

Particularly, none of the cited references discloses or suggests modifying an amide group-containing amino acid to one that does not contain an amide group. As admitted by the Office, Karger et al. does not disclose or suggest to those of ordinary skill in the art adding charged amino acid. Further, Karger et al. fails to disclose or suggest to those of ordinary skill in the art the step of modifying an amide group-containing amino acid to one that does not contain an amide group. While Fuchs et al. discloses charge modification by adding charged amino acid, it fails to disclose or suggest to those of ordinary skill in the art the step of modifying an amide group-containing amino acid to one that does not contain an amide group. Chen et al. also fails to cure the deficiency of Karger et al. and Fuchs et al., i.e.,

it fails to disclose or suggest to those of ordinary skill in the art the step of modifying an amide group-containing amino acid to one that does not contain an amide group.

The Office would fail to make a *prima facie* case for obviousness of the present claims. To establish a prima facie case for obviousness, the Office must satisfy *three* requirements: (1) the prior art relied upon must contain some suggestion or incentive, coupled with knowledge generally available in the art at the time of the invention, that would have motivated those of ordinary skill in the art to modify a reference or combine the references. See, *Karsten Mfg. Corp. v. Cleveland Gulf Co.*, 242 F.3d 1376, 1385, 58 USPQ2d 1286, 1293 (Fed. Cir. 2001) ("in holding an invention obvious in view of a combination of references, there must be some suggestion, motivation, or teaching in the prior art that would have led a person of ordinary skill in the art to select the references and combine them in a way that would produce the claimed invention."); (2) the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. In other words, hindsight analysis is not allowed. See *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991) ("While the idea of using a monkey gene to probe for a homologous human gene may have been obvious to try, many pitfalls existed that would have eliminated a reasonable expectation of successfully obtaining the EPO gene. Hindsight is not a justifiable basis on which to find that ultimate achievement of a long sought and difficult scientific goal was obvious."); *and* (3) the prior art reference or combination of references must teach or suggest all the limitations of the claims. See *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970) ("All words in a claim must be considered in judging the patentability of that claim against the prior art.").

The Office would fail to make a *prima facie* case for obviousness of the present claims because none of the three requirements is met here. Particularly, the cited references fail to teach or suggest all the limitations of the claims. For example, there is no teaching or suggestion in any of the cited references to those skilled in the art for modifying an amide group-containing amino acid into one that does not contain an amide group. When there is no teaching or suggestion for modifying an amide group-containing amino acid to an amino acid that does not contain an amide group, there cannot be a reasonable expectation of success in arriving at the presently claimed invention. Obviousness cannot be predicated on what is unknown. Furthermore, as discussed, there is no suggestion to make all three modifications (as presently recited) on one molecule.

Additionally, the presently claimed invention has unexpected or superior property. The Fab' antibody has uniform isoelectric point. Without wishing to be bound by any theory or mechanism, modification of the amide-containing amino acid to an amino acid which does not contain an amide group reduces microheterogeneity, a phenomenon which is responsible for diversity in isoelectric point. The Fab' antibody fragments prepared without modification of the amide group-containing amino acid shows diverged electrophoretic mobility as shown in Figure 3 of the present application. There is no reasonable expectation of success in arriving at the presently claimed invention. There is nothing in the cited references to reduce microheterogeneity.

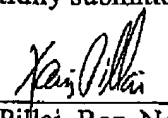
Moreover, as discussed in the specification, page 7, line 12-22, when performing the isoelectric focusing by the method disclosed in Shimura et al., the steps involved in obtaining an Fab' antibody having a uniform isoelectric point are complicated. In addition, when an isoelectric point of the antigen in the analyte is close to an isoelectric point of the fluorescently labeled antibody, migration time of the immune complex comprising the antigen and antibody becomes almost the same as that of the excessive antigen and/or antibody. Therefore, the electrophoretic peaks overlap significantly and detection cannot be performed with high accuracy. In contrast, the presently claimed invention provides superior performance, i.e., provides a method for quantitatively detecting an antigen which enables the analysis of the antigen with high accuracy, even when the isoelectric point of the antigen is close to that of the fluorescently labeled antibody. Bodmer et al. and Cabilly et al. do not cure the deficiency of Karger et al., Fuchs et al., Chen et al., or Shimura et al.

In view of all of the foregoing, applicants respectfully submit that the present claims, including claim 23, are patentable over the cited references.

Conclusion

A favorable decision is solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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